

Case Report

Carbamazepine Induced Asterixis with Hyperammonemia: A Case Report with Review of Literature

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ABSTRACT

Asterixis with hyperammonemia is an uncommon side-effect reported with carbamazepine. We report a case of carbamazepine induced asterixis with hyperammonemia and also the review of published literature on the same.

Key words: Asterixis, carbamazepine, hyperammonemia

INTRODUCTION

Carbamazepine is a commonly prescribed antiepileptic mood stabilizer for the treatment of acute manic and mixed episodes associated with bipolar I disorder and in neuropathic pain.^[1] Carbamazepine is also used off-label for the treatment of borderline personality disorder with affective dysregulation, impulsive-behavioral control, as well as agitation and aggression in patients with acquired brain injury.^[2] Common adverse effects include drowsiness, dizziness, gait instability, nausea, vomiting, hypotension, hyponatremia, elevated liver transaminases, nystagmus and confusion.^[3] Severe adverse reactions include aplastic anemia, agranulocytosis and dermatological reactions which include toxic epidermal necrosis and Stevens-Johnson syndrome.^[3] There are few case reports which report

both asterixis and hyperammonemia to be associated with use of carbamazepine.

Hyperammonemia is an uncommon adverse event that can lead to impaired consciousness, lethargy, coma and death. Early symptoms include appetite loss, nausea, insomnia, agitation, personality changes and clinical signs of hyperammonemia occur at concentrations $>60 \mu\text{mol/L}$.^[4] Decreased ammonia elimination can be secondary to hepatic failure, inherited defects of enzymes in the urea cycle, defects in fatty acid oxidation (carnitine deficiency), hematologic diseases and adverse effects of medications.^[5] Medications commonly associated with hyperammonemia include valproic acid, fluorouracil, salicylates, asparaginase^[6] and rarely with carbamazepine. Asterixis also known as “flapping tremors” means the inability to maintain a fixed posture against gravity and involves momentary lapses of posture, which are corrected immediately.^[7] Asterixis occurs typically in toxic-metabolic encephalopathies, commonly in hepatic coma, renal and pulmonary impairment, focal brain lesions (such as thalamic, parietal or mesencephalic) and as a symptom in overdose of various anticonvulsants.^[8] Asterixis has been reported as a presenting complaint in some cases with hyperammonemia.

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There have been a few cases which have reported hyperammonemia with the use of carbamazepine. Rittmannsberger and Leblhuber in their study have reported four patients with asterixis as a presentation of neurotoxicity at therapeutic doses of carbamazepine. Among the cases one patient was a 69-year-old woman with trigeminal neuralgia, who presented with asterixis at therapeutic levels of carbamazepine (800 mg/day) and had ammonia levels around 78 $\mu\text{mol/L}$. The other patient was a woman with mental retardation and epilepsy, who was on multiple antiepileptic medications which included phenytoin (200 mg/day), phenobarbital (100 mg/day) and carbamazepine (1200 mg/day).^[9] The other cases were diagnosed to have bipolar disorder and chronic schizophrenia being treated with a combination of psychotropic drugs like clozapine and lithium, developed asterixis after adding carbamazepine.^[9] Rivelli *et al.* have reported the development of asterixis with hyperammonemia in a patient with bipolar affective disorder who was on lithium, chlorpromazine and carbamazepine, with ammonia levels being 60 $\mu\text{mol/L}$.^[10] There have been few case reports which have presented with asterixis either by adding therapeutic doses of carbamazepine to a treatment regimen, or by increasing its dosage. Terzano *et al.* reported patients with a painful syndrome of central origin being treated with carbamazepine in which asterixis appeared with toxic serum levels. None of the above four patients had serum ammonia level being evaluated and most of the patients were on polypharmacy.^[11] In a study done by Adams *et al.* have reported a case of carbamazepine induced hyperammonemia without asterixis in a case of bipolar disorder at therapeutic levels of carbamazepine who was on polypharmacy with topiramate, olanzapine, desmopressine, quetiapine and carbamazepine.^[12] Ambrosetto *et al.* reported two patients who developed both hyperammonemia with asterixis with the use of carbamazepine at therapeutic doses.^[13]

To summarize the above case reports, most of the patients presented with hyperammonemia and asterixis after the use of carbamazepine, while few reports have not looked at the ammonia levels and only one case has increased ammonia levels in the absence of asterixis. We report a case of bipolar disorder who develop asterixis and confusion with the use of carbamazepine at therapeutic levels. Patient serum ammonia levels were elevated and clinical improvement occurred after discontinuation of carbamazepine.

CASE REPORT

This was a case report of a 31-year-old woman was admitted with a history of bipolar affective disorder of 2 years duration, presented with 6 weeks history of mixed

affective state. Family history was nil contributory and patient had partially responded to adequate trial of risperidone. Patient came from a lower socio-economic status and hence started on carbamazepine 200 mg/day which was increased up to 600 mg/day along with risperidone 6 mg/day orally. After 2 weeks of taking carbamazepine, the patient developed jerks in both upper limbs with asterixis and impaired sensorium. The patients liver function tests including the enzymes, renal parameters, complete blood count, serum electrolytes, thyroid function test and computed tomography of brain were within normal limits. The patient was tested negative for human immunodeficiency virus infection and syphilis. Her serum ammonia concentration was found to be 119 $\mu\text{mol/L}$ (normal reference level 11-35). Carbamazepine was discontinued and the patient regained her sensorium with absence of asterixis, whereas the serum ammonia level decreased to 47 $\mu\text{mol/L}$. Her carbamazepine levels were not done as she did not have any signs of carbamazepine toxicity except for asterixis and confusion. Subsequently patient was started on a combination of lithium and risperidone with adequate response.

DISCUSSION

There are certain observations that stand out in the present case which needs to be considered in our current understanding of carbamazepine induced hyperammonemia and asterixis. The above case describes an adult woman with bipolar illness who developed asterixis and hyperammonemia with the use of carbamazepine. When compared to earlier reports this patient was on risperidone which has not been associated with hyperammonemia. Temporal correlation of development of asterixis, confusion and elevated ammonia levels with the use of carbamazepine, which resolved completely with the discontinuation of medication indicate the causal relation between the drug and side-effects. There were no other clinical causes of hyperammonemia like hepatic failure, hematological disorders, though specific assessments related to inherited defects of enzymes in the urea cycle was not done. The presence of asterixis which typically occurs in toxic-metabolic encephalopathies, may be explained by the presence of hyperammonemia. Earlier reports reveal most cases of hyperammonemia along with asterixis. The possible mechanism of hyperammonemia due to carbamazepine is unknown and some researchers have postulated it to have a similar mechanism as that of valproic acid by disruption of urea cycle. An isolated increase in ammonia without an increase in liver enzymes indicates either hepatocellular dysfunction without cellular damage or isolated mitochondrial dysfunction. The treatment for hyperammonemia is to discontinue the

precipitant, as seen in the other reported cases involving carbamazepine. L-carnitine has been used in cases with urea cycle disorders and valproic-acid-related toxicities to reduce serum ammonia levels.^[4] Other conventional treatment options are also directed at lowering serum ammonia levels, which include the use of oral lactulose and consumption of a low-protein diet.^[4]

CONCLUSION

Based on the above case it can be concluded that carbamazepine induced hyperammonemia is not an uncommon side-effect and can present with the presence of asterixis and confusion.

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